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Behavioral and neurochemical sensitization to amphetamine following early postnatal administration of methylmercury (MeHg)☆

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Abstract

Perinatal exposure to methylmercury (MeHg) in rodents has been linked to changes in sensitivity to dopaminergic agents later in life. In an effort to determine the behavioral and neurochemical response to the indirect dopaminergic and serotonergic agonist amphetamine following neonatal exposure to MeHg, male BALB/c mice were administered MeHg during critical periods of neural development and challenged with amphetamine as adults. Mice were observed 15, 30 and 60 min after a single amphetamine injection (7.5 mg/kg i.p.) for presence of stereotypic and self-injurious behaviors, abnormal posture, and hyperthermia. Mice treated with 2 or 4 mg/kg MeHg on alternate days 3–15 of life demonstrated an increase in body temperature and the appearance of stereotypic and self-injurious behaviors not observed when amphetamine was administered to either vehicle-exposed mice or those treated with an equivalent total amount of MeHg administered on postnatal days 13 and 15. Neurochemical analysis of MeHg- and vehicle-exposed mice challenged with amphetamine or saline revealed alterations in dopaminergic and serotonergic activity which corresponded to the sensitized behavioral response to amphetamine. These observations demonstrate a critical window for MeHg exposure affecting the later appearance of amphetamine-induced self-injurious behavior and support the hypothesis that early exposure to environmental neurotoxicants may predispose individuals to engage in aberrant, intrusive behaviors later in life.

Keywords: Methylmercury; Amphetamine; Self-injurious behavior

1. Introduction

Aberrant, repetitive, stereotypic, and self-injurious behaviors (SIB) are observed in a number of neurodevelopmental disorders including autism, Rett Syndrome and Lesch-Nyhan Syndrome. Autism is the most prevalent of these disorders, affecting an estimated 1/166 individuals (Fombonne, 2003; Yeargin-Allsopp et al., 2003). Evidence suggests both a genetic and environmental component to the etiology of autism (Bernard et al., 2002; Lawler et al., 2004; Wassink et al., 2004). Since the exact etiology of autism remains unknown, the development of a comprehensive animal model which encompasses the core signs (impairments in communication and social interaction, presence of stereotypic behaviors) is essential but has remained problematic. We have devised a strategy in which behavioral manifestations of developmental disorders are characterized as "*retardations*" (i.e. behaviors fail to develop during a critical period), "*regressions*" (i.e. a behavior develops at approximately the right time but then is lost with further maturation), or "*intrusions*" (i.e. the appearance of behaviors aberrant in form or frequency (such as stereotypic or SIB) which mask the otherwise appropriate behaviors (Wagner et al., in press)). Within this framework, the effects of toxicant exposure are examined on tasks which target social, cognitive, and motor functioning at discrete points during development.

In previous studies, we administered amphetamine to mice to induce stereotypic and SIB, demonstrating that these intrusive behaviors are consequent to both dopaminergic and serotonergic activation and that the administration of risperidone, an

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antagonist of both systems, completely eliminates them without causing sedation (Halladay et al., 2003; Kita et al., 2000; Wagner et al., 2004). SIB occurs in as many as 70% of children with autism or autism spectrum disorders over their lifetime (Bartak and rutter, 1976; Dawson et al., 1998; Murphy et al., 1999) and in up to 40% of individuals in institutional settings (Eyman and Call, 1977; Saloviita, 2000).

In humans, adverse effects of developmental exposure to the environmental contaminant and heavy metal neurotoxicant, methylmercury (MeHg), include a delay in psychomotor development, abnormal reflexes, and sensorimotor and cognitive dysfunction (Gilbert and Grant-Webster, 1995; Goldey et al., 1994; Grandjean et al., 1997, 1998; Marsh et al., 1980). In rodents, deficits are also observed following early exposure to MeHg either during gestation and/or early postnatal development. These deficits are manifest as impairments in maze learning and retention, alterations in spontaneous motor activity, and delays in the development of normal reflexive behaviors (Baraldi et al., 2002; Chang and Annau, 1984; Dore et al., 2001; Gilbert et al., 1993; Goulet et al., 2003; Hughes and Sparber, 1978; Olson and Moush, 1975; Rice, 1998; Vorhees, 1985).

The immediate and long-term effects of MeHg administration on neurochemical function have been investigated. MeHg results in calcium-dependent release of serotonin (Oudar et al., 1989) and an inhibition of serotonin uptake *in vitro* (Dave et al., 1994). These effects were also seen *in vivo*, where administration of MeHg early in postnatal development produced an initial decrease in serotonin concentrations followed by an increase which persisted for up to 50 days (Lakshmana et al., 1993; Taylor and DiStefano, 1976; Zhou et al., 1999). Still lower doses of MeHg have been shown to alter synthesis of serotonin without affecting its steady-state levels (Sharma et al., 1982). In addition, there is an interaction of MeHg with the dopamine transporter leading to dopamine release (Bondy et al., 1979; Faro et al., 2002, 2003; Lakshmana et al., 1993). Exposure to MeHg during development has been shown to result in a change in responsiveness to dopamine agonists and antagonists in adults (Archer and Frederiksson, 1992; Cagiano et al., 1990; Eccles and Annau, 1982; Gimenez-Llort et al., 2001; Hughes and Sparber, 1978; Pereira et al., 1999; Rasmussen and Newland, 2001). This differential sensitivity of MeHg-exposed animals to dopaminergic agents in adulthood supports the hypothesis that effects of early MeHg exposure may be ''unmasked'' by later pharmacological challenge (Hughes and Sparber, 1978; Miller et al., 1973; Newland and Rasmussen, 2000).

While MeHg exposure has not been associated with the appearance of SIB, prenatal or early postnatal exposure of humans to MeHg through dietary sources has been linked to both delays in neurodevelopmental milestones and cognitive impairments during development (for reviews see Davidson et al., 2004; Gilbert and Grant-Webster, 1995). Therefore, the objective of the present study was to determine if early exposure to MeHg results a change in the intensity or frequency of the amphetamine-induced stereotypies including self-injurious behavior (SIB) later in life.

2. Materials and methods

2.1. Animals and treatment

Pregnant BALB/c mice (Taconic, NY) were housed in plastic cages in a temperature and humidity-regulated colony room with a 12 h light/12 h dark cycle and free access to food and water. All procedures were approved by the Rutgers University Animal Care and Facilities Committee; Rutgers is an AAALAC-accredited institution. Day of birth was recorded as postnatal day (PND) 0. Male pups were treated with phosphate buffered saline (PBS) ($n = 19$), or with 2.0 ($n = 9$) or 4.0 mg/kg ($n = 16$) MeHgCl (ICN, Costa Mesa) s.c. on alternate days between P3 and P15. A fourth group of pups received 8.0 mg/kg of MeHg on PND 13 and 15 only ($n = 9$). All mice were weaned at PND 25. On PND 125–130, mice were injected i.p. with either 7.5 mg/kg D-amphetamine sulfate (Sigma, St. Louis) or saline and observed for incidence of self-injurious behavior and rated on a stereotypy scale (see below). Immediately prior to saline or amphetamine administration (time 0) and then 15, 30 and 60 min after injection, body temperature was measured using a rectal probe coupled to a BAT-10 thermometer (Physitemp, Clinton, NJ). Mice were sacrificed immediately after body temperature was measured at the 60 min time point and the striatum and frontal cortex dissected and stored in liquid nitrogen until neurochemical assay by HPLC (Halladay et al., 1998).

2.2. Behavioral paradigms

2.2.1. Self-injurious behavior

Self-injurious behavior was recorded if a mouse was observed biting its front paws, limbs, or chest, or if it exhibited taffy-pulling of the skin during the 1 min observation period (Breese et al., 1984; Kita et al., 2000).

2.2.2. Stereotypy scale and limb splay

The stereotypy scale was modified from that of Kelly et al. (1975) and included digging, circling, sniffing, and vacuous chewing scored from 1 to 8 as follows: (1) not active; (2) some activity, sniffing; (3) bursts of stereotyped behavior over a large area in different places around the cage; (4) bursts of stereotyped behavior in one discrete area for the entire 1 min period; (5) continuous stereotyped behavior in one discrete area for the entire 1 min period; (6) bursts of vacuous chewing and oral dyskinesia; (7) continuous vacuous chewing in the same area for the entire 1 min period; (8) paw treading, either in bursts or continuously. The presence of limb splay was recorded if both the hind legs spread out beyond the width of its body. Piloerection and straub tail were also recorded, but were not consistently observed in any group.

2.3. Statistical analysis

2.3.1. SIB and limb splay

As each behavioral assessment of SIB and limb splay was made independently of the last observation (observations at

15 min did not carry over to 30 and 60 min time points), a binomial logistic regression was performed at each time point with drug treatment (PBS or MeHg at the three doses) serving as covariates. Only mice treated with amphetamine were included in the analysis, as no mouse exhibited SIB or limb splay in the absence of amphetamine. Variables which significantly contributed to the outcome ($p < 0.05$) were considered statistically significant. Incidence of SIB and limb splay were compared between MeHg and PBS exposed mice using a Fisher's Exact Test. Stereotypic behaviors at each time point were analyzed separately using a Kruskal–Wallis Test followed by a distribution free post-hoc test. Body temperature was analyzed using a repeated measures ANOVA across the four time points (time 0, 15, 30 and 60 min post-injection) followed by Fisher's PLSD at $p < 0.05$. Catecholamine and monoamine concentrations were analyzed using a one-way ANOVA followed by a Fisher's PLSD at $p < 0.05$.

3. Results

3.1. Self-injurious behavior

Using the Wald Statistic of the Beta coefficients in a block logistic regression, MeHg 2.0 mg/kg was associated with an increase of SIB at 15 min post-amphetamine injection ($\beta = 1.9$, $p = 0.03$) (Fig. 1). At 30 min post-amphetamine, both MeHg 2.0 and 4.0 mg/kg resulted in an increased incidence of SIB ($\beta = 2.4$, $p = 0.007$; $\beta = 1.6$, $p = 0.03$, respectively). At 60 min post-amphetamine, only MeHg 2.0 and MeHg 4.0 administered on PND 3–15 served as predictors of SIB ($\beta = 2.4$, $p = 0.007$; $\beta = 1.9$, $p = 0.01$, respectively).

3.2. Limb splay

Incidence of limb splay 15 min following amphetamine was predicted by treatment of MeHg at 2.0 mg/kg ($\beta = 3.1$, $p = 0.01$) (Fig. 2). At 60 min, an increased incidence of limb splay following amphetamine was seen in those groups exposed to MeHg at 4.0 mg/kg on PND 3–15 ($\beta = 3.8$, $p = 0.002$) and MeHg 8.0 on PND 13 and 15 only ($\beta = 2.4$, $p = 0.02$).

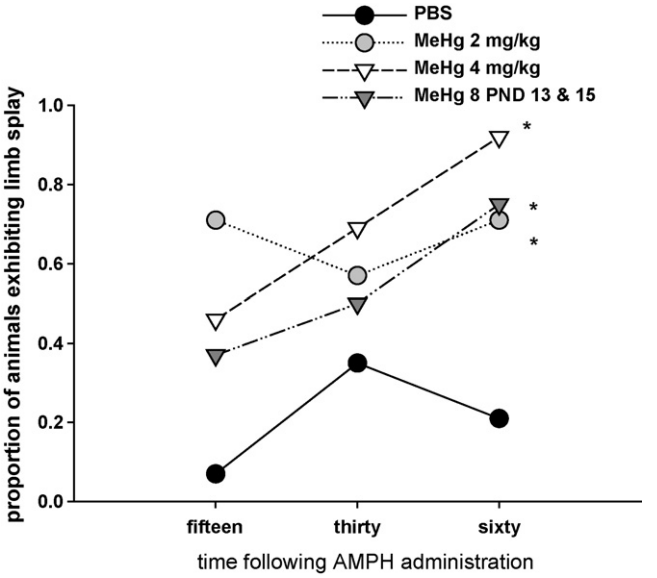

Fig. 2. Proportion of animals exhibiting hindlimb splay during 1 min observation periods at 15–60 min following i.p. injection of 7.5 mg/kg D-amphetamine. *Indicates significantly higher compared to those exposed to PBS as neonates using Fisher's Exact Test, $p < 0.05$.

3.3. Stereotypy score

There was a significant effect of group on stereotypy scores at 15, 30 and 60 min post-amphetamine ($H(3) = 13.2, p = 0.004$), ($H(3) = 18.1$, $p < 0.0001$) and ($H(3) = 20.8$, $p < 0.0001$), respectively (Fig. 3). A distribution free multiple comparison post-hoc test ($p < 0.05$) revealed significantly increased

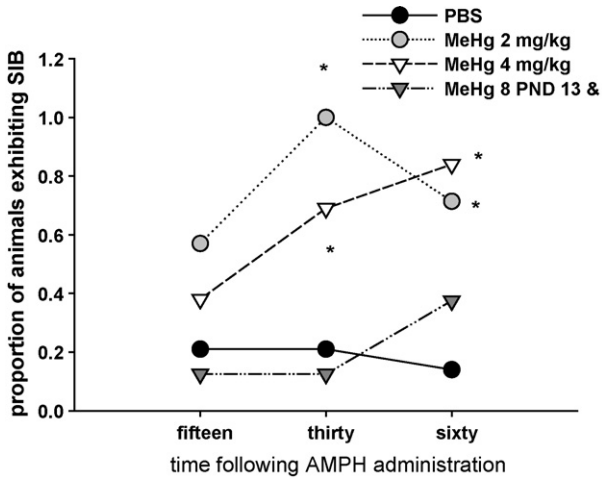

Fig. 1. Proportion of animals exhibiting self-injurious behavior during 1 min observation periods at 15–60 min following i.p. injection of 7.5 mg/kg D-amphetamine. *Indicates significantly higher compared to those exposed to PBS as neonates using Fisher's Exact Test, $p < 0.05$.

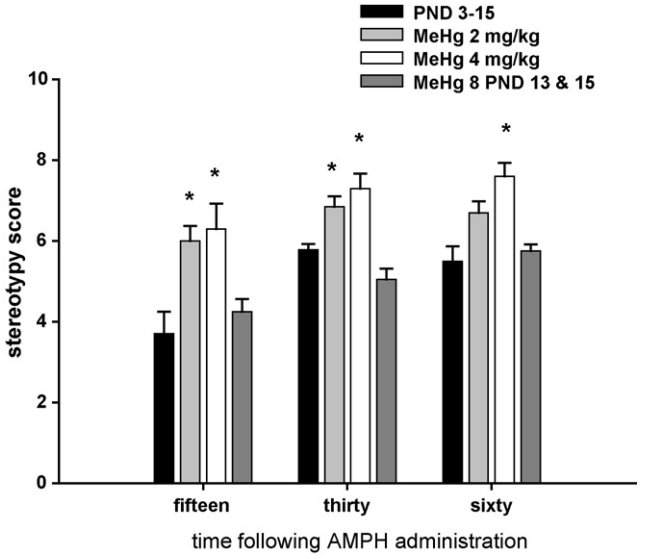

Fig. 3. Stereotypy scores following 7.5 mg/kg amphetamine in animals exposed to PBS or MeHg as neonates. *Indicates significantly higher compared to those exposed to PBS as neonates using a distribution free post-hoc test following a Kruskal–Wallis test, $p < 0.05$.

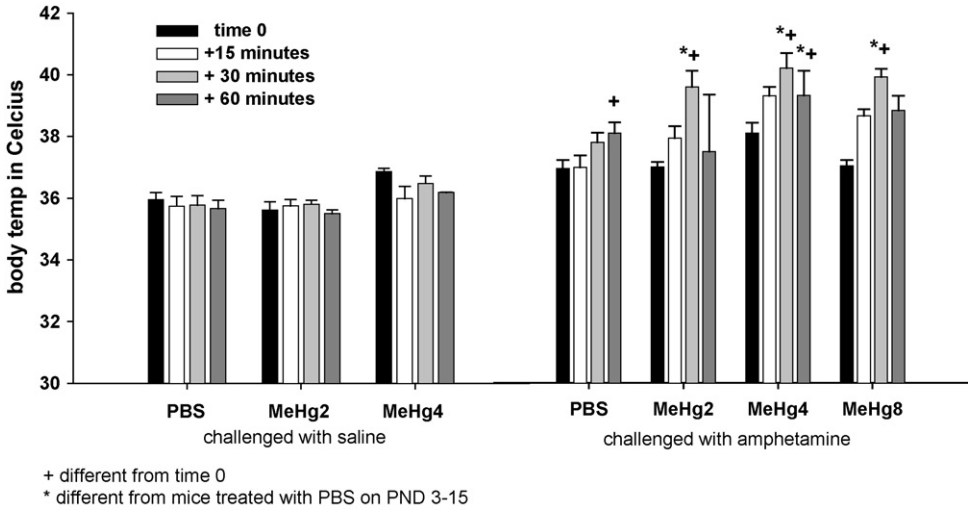

Fig. 4. Body temperature following either saline or 7.5 mg/kg amphetamine in animals exposed to PBS or MeHg as neonates. *Indicates significantly different from mice treated with PBS and challenged with amphetamine and +indicates significantly different from time 0 using Fisher's PLSD, $p < 0.05$.

stereotyped behaviors following amphetamine 15–30 min post-injection in mice exposed to 2.0 or 4.0 mg/kg MeHg as neonates. At 60 min post-injection, only those who were exposed to 4.0 mg/kg amphetamine showed significant elevations in stereotypy scores.

3.4. Body temperature

Amphetamine administration resulted in a significant elevation in body temperature in all groups ($F(1, 56) = 9$, $p = 0.004$) (Fig. 4). This effect was significant at 60 min post-injection in mice treated with PBS as neonates; however a significant elevation was observed at 30 min when mice were treated with MeHg 2.0 or 4.0 mg/kg on PND 3–15 ($F(3, 168) = 5, 8$, $p = 0.0001$). In addition, the amphetamine-induced rise in body temperature was greater in mice exposed to MeHg as neonates compared to PBS-pretreated mice.

3.5. Neurochemistry

3.5.1. Striatum

Striatal serotonin was slightly but non-significantly elevated following amphetamine in PBS pretreated mice; this increase was statistically significant when mice were pretreated with MeHg at 4.0 mg/kg on PND 3–15 ($F(1, 45) = 6.9$, $p = 0.012$). There was no difference in striatal 5-HIAA concentrations. The increase in 5HT concentrations without a reduction in 5-HIAA levels resulted in a decrease in 5-HIAA/5HT ratios following amphetamine in those mice exposed to MeHg 4.0 mg/kg as neonates ($F(3, 49) = 2.7$, $p = 0.05$, Fig. 5).

There were no significant effects of neonatal treatment (MeHg or PBS) or adult challenge (amphetamine or saline) on striatal dopamine (Fig. 6). Striatal DOPAC/DA were lowered all groups receiving amphetamine challenge ($F(1, 46) = 74.1$, $p < 0.0001$). Amphetamine challenge in adulthood produced

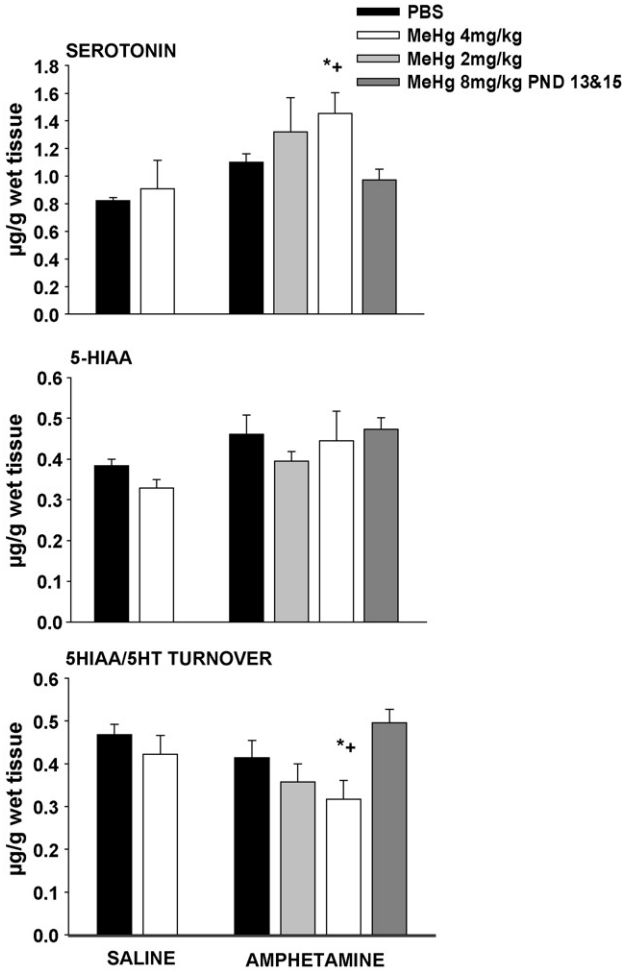

Fig. 5. Striatal serotonin concentrations (top), 5-HIAA concentrations (middle) and 5-HIAA/serotonin turnover ratios at 60 min following saline (left) or amphetamine (right) administration in animals exposed to PBS or MeHg as neonates. *Indicates significantly different from PBS exposed animals challenged with saline and +indicates significantly different from PBS exposed mice challenged with amphetamine using Fisher's PLSD, $p < 0.05$.

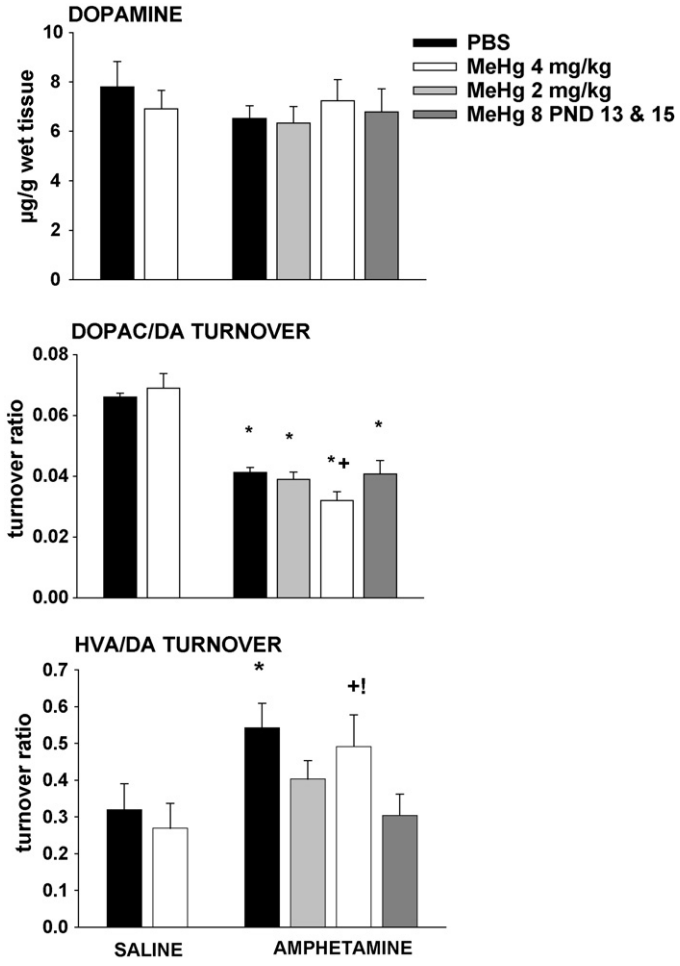

Fig. 6. Striatal dopamine concentrations (top), DOPAC/dopamine turnover (middle) and HVA/dopamine turnover ratios at 60 min following saline (left) or amphetamine (right) administration in animals exposed to PBS or MeHg as neonates. *Indicates significantly different from PBS exposed animals challenged with saline, +indicates significantly different from PBS exposed animals challenged with amphetamine and !indicates significantly different from MeHg-exposed animals challenged with saline using Fisher's PLSD, $p < 0.05$.

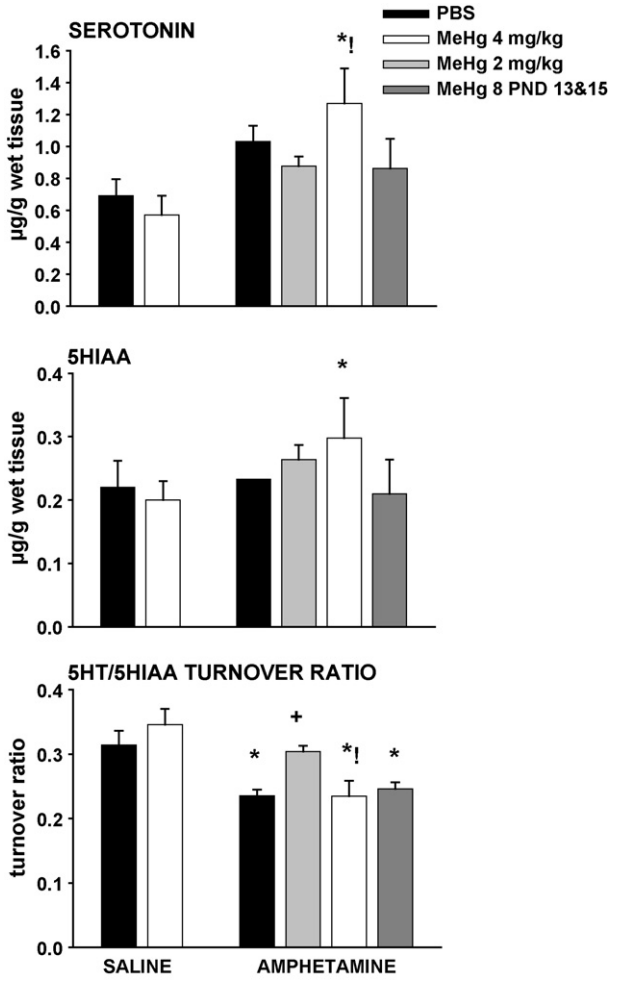

Fig. 7. Cortical serotonin concentrations (top), 5-HIAA concentrations (middle) and 5-HIAA/serotonin turnover ratios at 60 min following saline (left) or amphetamine (right) administration in animals exposed to PBS or MeHg as neonates. *Indicates significantly different from PBS exposed animals challenged with saline, +indicates significantly different from PBS exposed animals challenged with amphetamine and !indicates significantly different from MeHg-exposed animals challenged with saline using Fisher's PLSD, $p < 0.05$.

an increase in HVA/DA turnover ratio in both PBS and MeHg 4 mg/kg exposed mice ($F(1, 46) = 7.43$, $p = 0.009$).

3.5.2. Frontal cortex

Amphetamine challenge elevated cortical serotonin levels only in those mice exposed to 4.0 mg/kg MeHg as neonates ($F(1, 43) = 8$, $p = 0.007$). 5-HIAA/5HT ratios were reduced following amphetamine in those groups who were neonatally exposed to PBS or to 4.0 mg/kg MeHg or 8.0 mg/kg MeHg ($F(1, 41) = 43.6$, $p < 0.0001$) (Fig. 7).

Following neonatal exposure to 4.0 mg/kg MeHg, cortical dopamine levels were reduced and DOPAC/DA levels elevated compared to PBS-treated mice ($F(3, 43) = 6.4$, $p = 0.001$) and ($F(3, 41) = 0.04$) (Fig. 8). While amphetamine did not significantly affect dopamine or DOPAC levels in the cortex of PBS-treated mice, amphetamine challenge significantly elevated levels of both dopamine ($F(1, 43) = 9.6$, $p = 0.003$) and DOPAC ($F(1, 43) = 3.9$, $p = 0.05$). HVA/DA turnover ratios were elevated in groups receiving amphetamine following neonatal exposure to PBS, MeHg 2.0 mg/kg on PND 3–15 and MeHg 8.0 on PND 13 and 15. There was no significant elevation in HVA/DA following amphetamine in mice treated with MeHg 4 mg/kg as neonates ($F(1, 41) = 4.1$, $p = 0.04$).

4. Discussion

Early exposure to MeHg primed the mice such that there was an enhanced sensitivity to a later injection of amphetamine to induce intrusive SIB. In addition, a critical early period (PND 3–13) was identified for this effect, as a higher total dose of MeHg administered later in development (PND 13 and 15) did not result in the increased sensitivity to the amphetamine. The response to MeHg administered early in life was not dose-dependent (2 and 4 mg/kg MeHg resulted in a similar response to amphetamine in adulthood). Rather, the critical period of exposure during neurodevelopment seemed to be more important, evidenced by the lack of

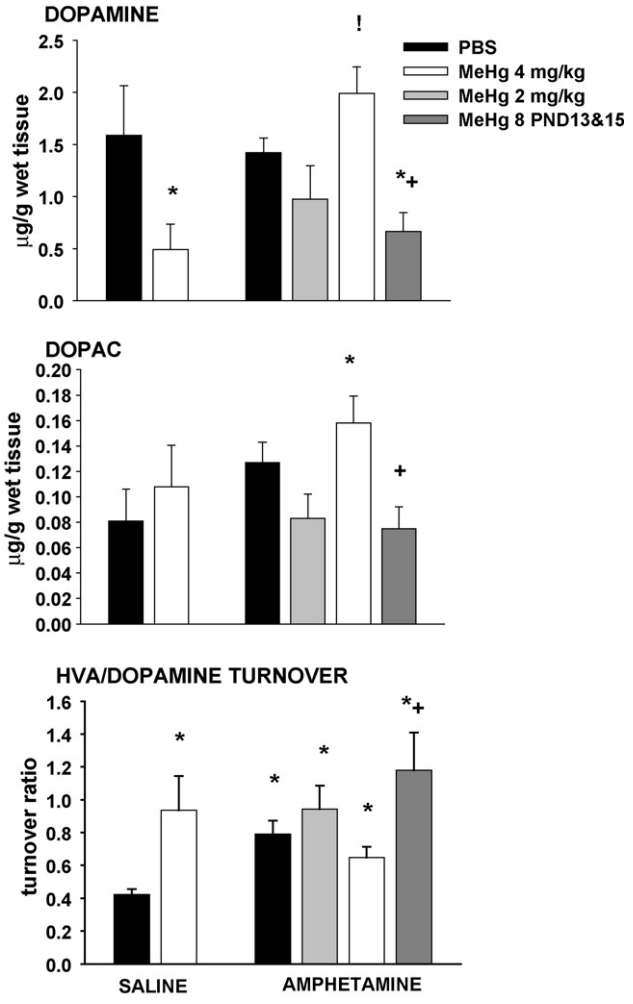

Fig. 8. Cortical dopamine concentrations (top), DOPAC concentrations (middle) and HVA/dopamine turnover ratios at 60 min following saline (left) or amphetamine (right) administration in animals exposed to PBS or MeHg as neonates. *Indicates significantly different from PBS exposed animals challenged with saline, +indicates significantly different from PBS exposed animals challenged with amphetamine and !indicates significantly different from MeHg-exposed animals challenged with saline using Fisher's PLSD, $p < 0.05$.

sensitization to amphetamine when a higher dose of MeHg was administered on PND 13 and 15 only. Other studies have reported the importance of exposure period on the neurobehavioral effect of MeHg during development (Dore et al., 2001; Rice and Barone, 2000). These data indicate that toxicant exposure early in life may prime an individual, rendering it sensitive to the deleterious effects of later exposures to the same or different agents.

In addition to the stereotypic and SIB, MeHg-treated mice were more likely to exhibit hindlimb splay and increased body temperature following amphetamine. These behaviors were rarely observed following this dose of amphetamine administered to the control mice. However, in contrast to the stereotypic and SIB, an increased incidence of limb splay following amphetamine administration was observed when mice were exposed to MeHg on PND 13 and 15. Hindlimb splay is a hallmark of the serotonin syndrome induced by direct and indirect serotonergic agonists (Borsini and Brambilla, 2001; Jacobs, 1976; Sallinen et al., 1998). Although mice exposed at 2 mg/kg MeHg at PND 3–15 seemed to be the most sensitive to amphetamine-induced hindlimb splay, all MeHg-exposed mice showed an increased incidence of this behavior by 60 min post-amphetamine injection. Likewise, all mice exposed to MeHg as neonates, regardless of dose or exposure period, showed an enhanced hyperthermic response to amphetamine. The rise in body temperature occurred earlier (30 min) and was more intense compared to those treated with PBS as neonates.

Tissue concentrations of dopamine, serotonin and their metabolites were measured 60 min after amphetamine administration, a time point at which amphetamine enhanced SIB in mice exposed to MeHg as neonates. Serotonin concentrations were only slightly elevated by amphetamine in PBS-treated mice but significantly increased in mice exposed to MeHg. In addition, amphetamine-induced changes in the DOPAC/DA ratio were significantly reduced in mice previously exposed to MeHg. While amphetamine elevated HVA/DA turnover in the striatum, this effect was attenuated in those mice receiving prior MeHg exposure. In the frontal cortex, neonatal MeHg exposure resulted in a significant reduction in dopamine concentrations, an effect that was reversed by amphetamine administration, and not observed in mice treated with PBS as neonates.

In general, the enhancement of amphetamine-related changes in striatal and cortical monoamine concentrations in mice exposed to MeHg as neonates is consistent with augmentation of amphetamine-induced behaviors, including SIB and stereotypy. The mechanism through which early MeHg exposure altered the behavioral and neurochemical response to the later amphetamine challenge is unknown but may involve changes in monoamine oxidase activity or alterations in neuronal activity (Chakrabarti et al., 1998; Gulley et al., 2004; Rebec et al., 1997; Stamler et al., 2004). Alternatively, the change in dopamine and serotonergic activity following early toxicological injury may produce hypersensitivity to monoaminergic agonists as adults through receptor mediated mechanisms (el Mansari et al., 1994).

The results of this study are consistent with earlier studies which demonstrate behavioral sensitization to amphetamine following early MeHg exposure (Archer and Frederiksson, 1992; Cagiano et al., 1990). The higher stereotypy scores following MeHg exposure represents the appearance of focused oral dyskinesias in this group, a behavior which was not observed following amphetamine administration in PBS exposed mice. Drug challenge has proven to be an effective strategy to unmask behavioral deficits that are not otherwise apparent following prior toxicant exposure (Duffard and Duffard, 2002; Halladay et al., 2000; McCann and Ricuarte, 1993; Newland and Rasmussen, 2000; Virgolini et al., 2004). Therefore, while not resulting in overt behavioral symptomatology, early environmental toxicant exposure may produce behavioral sensitization leading to the later appearance of intrusive SIB.

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